PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Daratumumab, Bortezomib, Thalidomide and Dexamethasone MYELOMA

PROTOCOL REF: MPHADBTD
(Version No. 1.0)

Approved for use in:

- Newly diagnosed myeloma patients who are eligible for high dose chemotherapy with autologous stem cell transplant.

Blueteq submission is required

Dosage:

Drug	Dosage	Route	Frequency
Cycle 1 and 2 (28 day cycles)			
Daratumumab	1800mg	S/C	Days 1, 8, 15 and 22
Bortezomib	1.3mg/m^2	S/C	Days 1, 4, 8 and 11
Dexamethasone	40mg	PO	Days 1&2, 8&9, 15&16, 22&23
Thalidomide	50 to 100mg	PO nocte	Days 1 to 28
Cycle 3 and 4 (28 day cycles)			
Daratumumab	1800mg	S/C	Day 1 and 15
Bortezomib	1.3mg/m^2	S/C	Days 1, 4, 8 and 11
Dexamethasone	40mg	PO	Days 1&2
Dexamethasone	20mg	PO	Days 8&9 and 15&16
Thalidomide	50 to 100mg	PO nocte	Days 1 to 28

Drug	Dosage	Route	Frequency
Cycle 5 and 6 (28 day cycles) Post Transplant			
Daratumumab	1800mg	S/C	Days 1 and 15
Bortezomib	1.3mg/m^2	S/C	Days 1, 4, 8 and 11
Dexamethasone	20mg	PO	Days 1&2, 8&9, 15&16
Thalidomide	50 to 100mg	PO nocte	Days 1 to 28

Bortezomib can be administered weekly on days 1, 8, 15 and 22 of a 28 day cycle if they cannot tolerate twice weekly dosing above.

Max 6 cycles

Administration and counselling points:

- Injection related reactions can occur with daratumumab – see toxicity section for details
- Daratumumab can reactivate hepatitis B so a hepatitis B screen is required prior to starting treatment
- Daratumumab may cause a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. See SPC for further information.
- Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.
- In the event of a planned transfusion blood transfusion centres should be notified of daratumumab interference with indirect antiglobulin tests. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices
- When a patient is counselled the specialist nurse needs to inform the RLUH's haematology lab that the patient is being started on daratumumab.
- Prophylactic anticoagulation is required throughout treatment due to thrombotic effect of thalidomide.
- There must be a gap of at least 72 hours between bortezomib doses.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention program and provide patients with appropriate patient educational brochure and patient card.

- A thalidomide treatment initiation form (TIF) must be completed prior to initiation of thalidomide and prescription authorisation form (PAF) must be completed prior to each thalidomide prescription as detailed in the Celgene pregnancy prevention program.
- Daratumumab injection-related reactions (IRRs)

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- Allopurinol PO 300mg daily (cycle 1 only)
- Omeprazole PO 20mg daily
- Aciclovir PO 400mg twice daily
- Co-trimoxazole PO 480mg daily
- Anticoagulation – options include prophylactic dose of low molecular weight heparin (LWMH) (dalteparin 5000 units s/c OD) and treatment dose of LMWH in high risk patients. For patients established on DOACs, patients may continue DOAC treatment or be switched to a LMWH.
- Metoclopramide PO 10mg TDS PRN
- Nystatin 1ml four times a day
- Chlorhexidine mouthwash 10ml twice a day

<u>Daratumumab pre-infusion medication prior to all cycles</u>

To be administered at least 1 hour prior to daratumumab infusion:

- Montelukast 10mg PO STAT (prior to cycle 1 only but continue if COPD/Asthma)
- Paracetamol 1000mg PO STAT
- Chlorphenamine 4mg PO STAT
- Dexamethasone PO STAT (dose dependant on stage of therapy)

Interactions:

Daratumumab

There are no known drug interactions with daratumumab

Thalidomide

Thalidomide has sedative properties, thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 antihistamines, opiate derivatives, barbiturates and alcohol. Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness.

Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.

Combined oral contraceptives are not recommended due to the increased risk of venous thromboembolic disease.

Bortezomib

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) because they may increase the plasma concentration of bortezomib.

The concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as they may decrease the plasma concentration of bortezomib.

During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

For more detailed interactions please refer to the SPC

Treatment schedule cycles 1 and 2:

Day	Drug	Dose	Route	Diluent and rate
1	**Montelukast**	**10mg**	**PO**	1 hour prior to daratumumab
	Paracetamol	**1g**	**PO**	
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**40mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
	Bortezomib	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
Days 1 to 28	**Thalidomide**	**50-100mg**	**PO**	Nocte
2	**Dexamethasone**	**40mg**	**PO**	
4	**Bortezomib**	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
8	**Montelukast**	**10mg**	**PO**	1 hour prior to daratumumab
	Paracetamol	**1g**	**PO**	
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**40mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
	Bortezomib	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
9	**Dexamethasone**	**40mg**	**PO**	
11	**Bortezomib**	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
15	**Montelukast**	**10mg**	**PO**	1 hour prior to daratumumab
	Paracetamol	**1g**	**PO**	
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**40mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
16	**Dexamethasone**	**40mg**	**PO**	
22	**Montelukast**	**10mg**	**PO**	1 hour prior to daratumumab
	Paracetamol	**1g**	**PO**	
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**40mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
23	**Dexamethasone**	**40mg**	**PO**	

Treatment schedule cycle 3 and 4

Day	Drug	Dose	Route	Diluent and rate
1	**Montelukast**	**10mg**	**PO**	Only if asthma/COPD
	Paracetamol	**1g**	**PO**	1 hour prior to daratumumab
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**40mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
	Bortezomib	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
Days 1 to 28	**Thalidomide**	**50-100mg**	**PO**	Nocte
2	**Dexamethasone**	**40mg**	**PO**	
4	**Bortezomib**	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
8	**Dexamethasone**	**20mg**	**PO**	
	Bortezomib	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
9	**Dexamethasone**	**20mg**	**PO**	
11	**Bortezomib**	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
15	**Montelukast**	**10mg**	**PO**	Only if asthma/COPD
	Paracetamol	**1g**	**PO**	1 hour prior to daratumumab
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
16	**Dexamethasone**	**20mg**	**PO**	

Treatment schedule cycle 5 and 6

Day	Drug	Dose	Route	Diluent and rate
1	**Montelukast**	**10mg**	**PO**	Only if asthma/COPD
	Paracetamol	**1g**	**PO**	1 hour prior to daratumumab
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
	Bortezomib	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
Days 1 to 28	**Thalidomide**	**50-100mg**	**PO**	Nocte
2	**Dexamethasone**	**20mg**	**PO**	
4	**Bortezomib**	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
8	**Dexamethasone**	**20mg**	**PO**	
	Bortezomib	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
9	**Dexamethasone**	**20mg**	**PO**	
11	**Bortezomib**	**1.3mg/m^2**	**S/C**	Over 3 to 5 seconds
15	**Montelukast**	**10mg**	**PO**	Only if asthma/COPD
	Paracetamol	**1g**	**PO**	1 hour prior to daratumumab
	Chlorphenamine	**4mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
	Daratumumab	**1800mg**	**S/C**	Over 3 to 5 minutes
16	**Dexamethasone**	**20mg**	**PO**	

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, drowsiness, venous thromboembolism, peripheral neuropathy, injection site reactions, infusion related reactions, high blood sugars, teratogenicity

Investigations and treatment plan:

	Pre	Cycle 1	Before each dose of daratumumab	Before each dose of bortezomib	Cycle 2	Cycle 3 onwards	Ongoing
Informed Consent	X						
Clinical Assessment	X	X			X	X	
SACT Assessment	X	X	X	X	X	X	Prior to every dose
On treatment review			X				
Blood pressure/ Pulse/ Temperature/ Respiratory rate			X				Continuously monitored during daratumumab infusion
FBC. U&E, LFTs, bone profile	X	X			X	X	Blood should be taken within 7 days of day 1 of every cycle
Creatinine clearance calculated	X	X			X	X	Blood should be taken within 7 days of day 1 of every cycle
HbA1C	X						Repeat as clinically indicated
B2Microglobulin	X						
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X			X	X	Prior to every cycle
Red cell phenotype (notify transfusion lab)	X						
Hepatitis B/C serology	X						
PS recorded	X	X			X	X	Prior to every cycle
Pregnancy test	X						As clinically indicated
Thalidomide prescription authorization form		X					With every prescription
Neurological assessment (for neuropathy)	X	X			X	X	

Height recorded	X						
Weight recorded	X	X			X	X	Prior to every cycle
Imaging as per NICE/network guidance and clinical indication	X						To restage as indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

If cytopenias are due to disease, treatment can proceed providing this is clearly documented.

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Platelet ≥ 25 x 10^9/L

Once the symptoms of the toxicity have resolved, bortezomib treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dosing in renal and hepatic impairment:

Renal	**Daratumumab:** No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment.
	Bortezomib: No dose reductions necessary if eGFR >20ml/min Unknown PK data in patients with severe renal impairment not undergoing dialysis Dialysis may reduce bortezomib concentrations and therefore should be administered after dialysis

<table>
<tr><td></td><td colspan="4">Thalidomide: Thalidomide Celgene has not formally been studied in patients with impaired renal function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.</td></tr>
<tr><td rowspan="6">Hepatic</td><td colspan="4">Daratumumab: No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment.</td></tr>
<tr><td colspan="4">Thalidomide: Thalidomide Celgene has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.</td></tr>
<tr><td colspan="4">Bortezomib: Metabolised by liver enzymes and therefore dose reductions required in moderate to severe impairment.</td></tr>
<tr><td>Grade of hepatic impairment</td><td>Bilirubin</td><td>ALT / AST</td><td>Modification of starting dose</td></tr>
<tr><td rowspan="2">Mild</td><td>≤1.0 x ULN</td><td>>ULN</td><td>None</td></tr>
<tr><td>>1.0 x-1.5 x ULN</td><td>Any</td><td>None</td></tr>
<tr><td>Moderate</td><td>>1.5 x- 3x ULN</td><td>Any</td><td rowspan="2">Reduce bortezomib to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability</td></tr>
<tr><td>Severe</td><td>>3.0 x ULN</td><td>Any</td></tr>
</table>

Peripheral Neuropathy

Bortezomib	
If there are symptoms of peripheral neuropathy the dose reduction schedule below must be invoked. Bortezomib should be stopped if symptoms or signs progress despite this	
Grade 1 with pain or grade 2	Reduce to 1.0mg/m^2 or reduce to 1.3mg/m^2 weekly (day 1 and 8)
Grade 2 with pain of grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7mg/m^2 weekly (day 1 and 8)
Grade 4 and/or severe autonomic neuropathy	Discontinue

Thalidomide	
Severity of neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function	Consider reducing dose if symptoms worsen. Dose reduction is not necessarily followed by improvement of symptoms.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose / interrupt treatment and continue to monitor. Discontinue if no improvement or continued worsening of the neuropathy. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted.
Grade 3 (interfering with activities of daily living) or Grade 4 (disabling neuropathy)	Discontinue treatment

Daratumumab Injection related reactions:

Injection-related reactions (IRRs) can happen when daratumumab is administered. Monitor patients throughout the injection and the post-injection period (especially during the first and second injections). The following monitoring requirements schedule should be followed;

First infusion:

Monitor patient for 4 hours post infusion including blood pressure, pulse, temperature and respiratory rate pre-injection and every 30 minutes thereafter

Second and Subsequent infusions:

There is no need to routinely monitor blood pressure, pulse, temperature and respiratory rate. Keep patients for 30 minutes after injection, can be sent home if feel well. **Note patients should be kept for longer if they experienced a grade 2+ IRR during their previous infusion.**

Severe reactions can occur, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema and pulmonary oedema. Symptoms noted predominantly included

nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus and hypotension.

Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with daratumumab.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

Medical management/supportive treatment for IRRs should be instituted as needed. Daratumumab therapy should be permanently discontinued in the event of life-threatening IRRs.

References:

1. https://www.medicines.org.uk/emc Daratumumab
2. https://www.medicines.org.uk/emc Bortezomib
3. https://www.medicines.org.uk/emc Thalidomide
4. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; **20:** e201–08.
5. BNF available via: https://bnf.nice.org.uk/
6. NICE: TA763: Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable. Published date: February 2022.

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Jennifer Gibson	V1.0